

US009181257B2

# (12) United States Patent Honigberg et al.

# (54) INHIBITORS OF BRUTON'S TYROSINE KINASE

(71) Applicant: **Pharmacyclics, Inc.**, Sunnyvale, CA

(US)

(72) Inventors: Lee Honigberg, San Francisco, CA

(US); Erik Verner, Belmont, CA (US);

Zhengying Pan, Austin, TX (US)

(73) Assignee: PHARMACYCLICS LLC, Sunnyvale,

CA (US)

(\*) Notice: Subject to any disclaimer, the term of this

patent is extended or adjusted under 35

U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-

claimer.

(21) Appl. No.: 14/080,640

(22) Filed: Nov. 14, 2013

(65) **Prior Publication Data** 

US 2014/0171453 A1 Jun. 19, 2014

### Related U.S. Application Data

Continuation of application No. 14/033,344, filed on Sep. 20, 2013, which is a continuation of application No. 13/952,531, filed on Jul. 26, 2013, now Pat. No. 8,759,516, which is a continuation of application No. 13/890,498, filed on May 9, 2013, which is a continuation of application No. 13/849,399, filed on Mar. 22, 2013, now Pat. No. 8,975,266, which is a continuation of application No. 13/654,173, filed on Oct. 17, 2012, now Pat. No. 8,957,079, which is a continuation of application No. 13/542,440, filed on Jul. 5, 2012, now Pat. No. 8,754,091, which is a continuation of application No. 13/479,053, filed on May 23, 2012, now Pat. No. 8,697,711, which is a continuation of application No. 13/472,292, filed on May 15, 2012, now Pat. No. 8,691,546, which is a continuation of application No. 13/450,158, filed on Apr. 18, 2012, now Pat. No. 8,748,439, which is a continuation of application No. 13/361,733, filed on Jan. 30, 2012, now Pat. No. 8,399,470, which is a continuation of application No. 13/340,409, filed on Dec. 29, 2011, now Pat. No. 8,748,438, which is a continuation of application No. 13/335,719, filed on Dec. 22, 2011, now Pat. No. 8,735,404, which is a continuation of application No. 13/328,718, filed on Dec. 16, 2011, now Pat. No. 8,476,284, which is a continuation of application No. 13/312,606, filed on Dec. 6, 2011, now Pat. No. 8,497,277, which is a continuation of application No. 13/249,066, filed on Sep. 29, 2011, now Pat. No. 8,735,403, which is a continuation of application No. 12/356,498, filed on Jan. 20, 2009, now Pat. No. 8,088,781, which is a continuation of application No. 11/617,645, filed on Dec. 28, 2006, now Pat. No. 7,514,444.

(10) Patent No.: US 9,181,257 B2

(45) **Date of Patent:** \*Nov. 10, 2015

(60) Provisional application No. 60/826,720, filed on Sep. 22, 2006, provisional application No. 60/828,590, filed on Oct. 6, 2006.

(51) Int. Cl.

A01N 43/90 (2006.01)

A61K 31/519 (2006.01)

C07D 487/00 (2006.01)

C07D 487/04 (2006.01)

A61K 31/00 (2006.01)

A61K 45/06 (2006.01)

A61K 9/48 (2006.01)

(52) U.S. Cl.

(58) Field of Classification Search

None

See application file for complete search history.

#### (56) References Cited

#### U.S. PATENT DOCUMENTS

5,397,787 A 6,160,010 A 6,221,900 B1 6,326,469 B1 6,506,769 B2 6,660,744 B1 6,753,348 B2 6,770,639 B2	3/1995 12/2000 4/2001 12/2001 1/2003 12/2003 6/2004 8/2004	Buzzetti Uckun et al. Uckun et al. Ullrich et al. Snow et al. Hirst et al. Uckun et al. Snow et al.

# (Continued)

# FOREIGN PATENT DOCUMENTS

EP 1473039 11/2004 WO WO-97-28161 8/1997

# (Continued) OTHER PUBLICATIONS

U.S. Appl. No. 14/340,483, filed Jul. 24, 2014, Honigberg et al.

Primary Examiner — Jeffrey H Murray (74) Attorney, Agent, or Firm — Wilson Sonsini Goodrich & Rosati

(Continued)

### (57) ABSTRACT

Disclosed herein are pyrazolo[3,4-d]pyrimidines that form covalent bonds with Bruton's tyrosine kinase (Btk). Also described are irreversible inhibitors of Btk. Methods for the preparation of the compounds are disclosed. Also disclosed are pharmaceutical compositions that include the compounds. Methods of using the Btk inhibitors are disclosed, alone or in combination with other therapeutic agents, for the treatment of autoimmune diseases or conditions, heteroimmune diseases or conditions, cancer, including lymphoma, and inflammatory diseases or conditions.

## 14 Claims, 8 Drawing Sheets